Biopharmaceutical Cold Chain Management

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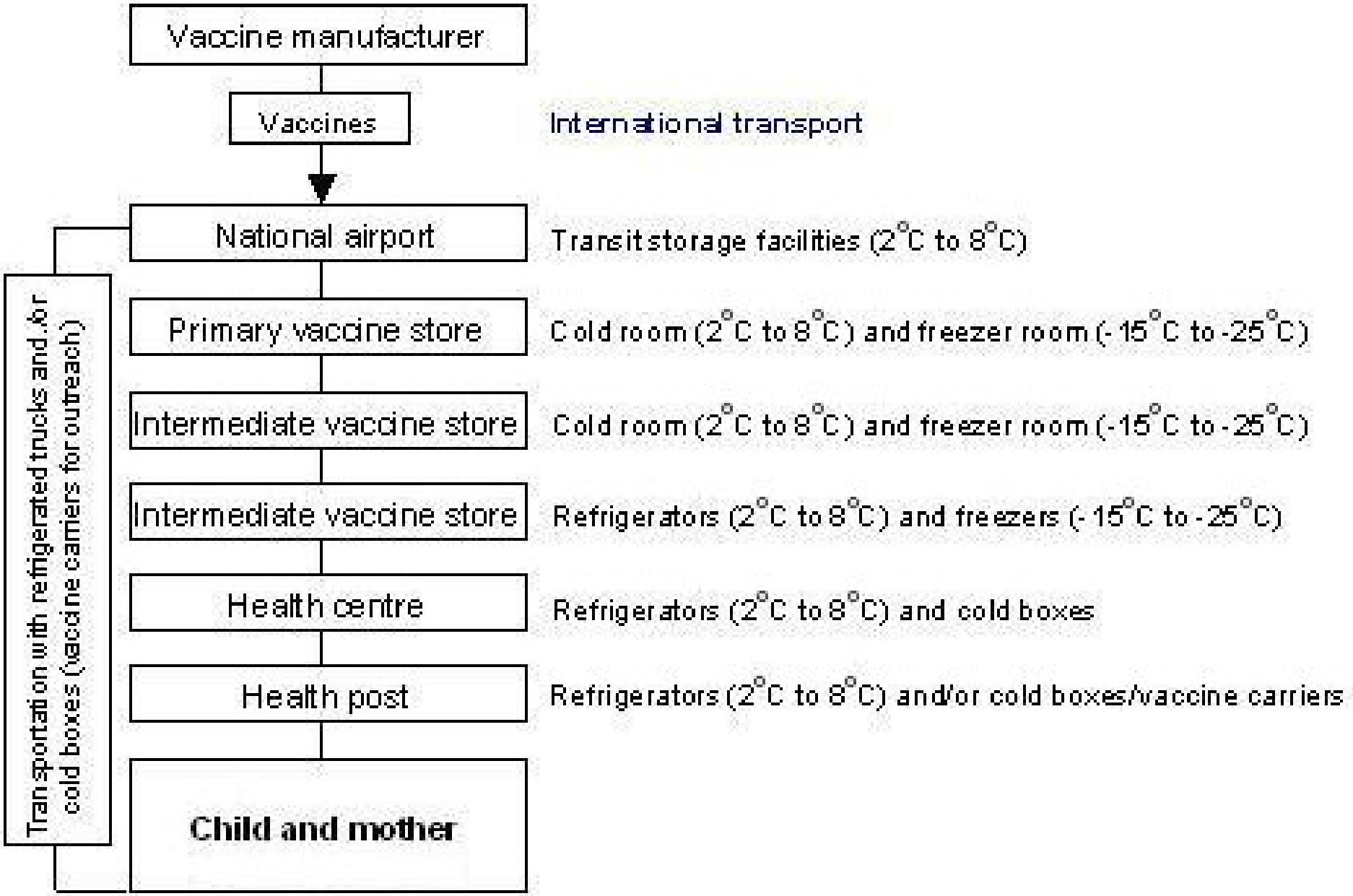
Disclaimer

- The views expressed during this presentation are my own and may not be those of the FDA.

Overview

- Introduction
- Need for controlled storage
- Holding and distribution
- Cold storage equipment maintenance
- Cold storage and stability
- Evaluation on inspection
- Conclusion


NEVER FROZEN
FROZEN/ THAWED
IMMEDIATELY AFTER SHAKING
Smooth and cloudy
Not smooth, granular particles
30 MINUTES AFTER SHAKING
Starting to clear
No sediment
Almost clear
Thick sediment
USE VACCINE
DO NOT USE VACCINE


Vaccine manufacturer
Vaccines
International transport
National airport
Transit storage facilities (2°C to 8°C)
Primary vaccine store
Cold room (2°C to 8°C) and freezer room (-15°C to -25°C)
Intermediate vaccine store
Cold room (2°C to 8°C) and freezer room (-15°C to -25°C)
Intermediate vaccine store
Refrigerators (2°C to 8°C) and freezers (-15°C to -25°C)
Health centre
Refrigerators (2°C to 8°C) and cold boxes
Health post
Refrigerators (2°C to 8°C) and/or cold boxes/vaccine carriers
Child and mother
Transportation with refrigerated trucks and/or cold boxes (vaccine carriers for outreach)

Introduction

- Where did the phrase “Cold Chain” come from?
  - Cold – need to control temperature to prevent growth of microbial organisms in food
  - Chain – stems from “chain of custody”
- 1990’s HACCP rules as a systematic approach to food safety

Introduction

- The “Cold Chain” concept for biopharmaceuticals has been around since the FD&C Act and cGMPs were enacted by congress
- The “Cold Chain” terminology was adopted for such products after the food HCAAP rules were published

Introduction

- The terminology of Cold Chain Management has evolved over time – but it still means that temperature is controlled from the cell substrate to the distributor to the end user
- “Cold Chain” as referenced in this talk begins with the starting material through to the final product storage, shipment and stability storage

Introduction

- Storage of biopharmaceutical products occurs at different stages in the process
  - Storage of cell banks
  - Storage of intermediates (short term)
  - Storage of final formulated bulks (APIs) (years at a time)
  - Storage of final product
  - Storage of stability samples
  - Storage at the distributor

Introduction

- Focus on the laws and guidance that apply to temperature controls during the manufacture, storage, shipment, and stability of product intermediates and final product
- Examples of breaks in the “Cold Chain”

Introduction

- The cGMP regulations include control of product storage and maintenance of storage equipment
- FDA and ICH Guidance documents make reference to storage controls from the starting point of a product to distribution and stability

Need for Controlled Storage

- Many biopharmaceutical products require storage at a specified temperature to prevent degradation, which may lead to a loss in potency
- Variability in the storage and shipping temperature may affect the quality of the product through its life time from the start of manufacturing to the distribution of the final product.

Need for Controlled Storage

- It is the Law! FD&C Act Sec 501(a)(2)(B) states, “A drug or device shall be deemed to be adulterated: if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with CGMP.....”

Need for Controlled Storage

- **Preamble for** Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding:
  - 510: One comment argued that 211.208 is contradictory in that it prohibits salvaging and return of drug products to the marketplace when the drug products have been exposed to improper storage conditions.
  - Commissioner disagrees. The purpose of this section is to provide appropriate procedures for determining suitability of salvaging of the drug products that may have been exposed to such conditions.

Need for Controlled Storage

- Regulations are in place that require specified storage temperatures for specific products
- General Biological Product Standards 610's
  - 21 CFR 610.53(c), Table of dating periods for specific products at required temperature, examples include (not limited to):
    - Immune Globulins 1-5 °C
    - MMR live vaccine -20 °C
    - Albumin 0 °C or colder
    - Pertussis Vaccine 1-5 °C

Need for Controlled Storage

- 640's Subpart H - Albumin
  - 21 CFR 640.80(d) "Bulk concentrate to be held for more than one week prior to further processing shall be stored... at a temperature of –5 °C or colder."

Need for Controlled Storage

- The CMC Guidance documents for different classes of biologics state that the storage of cell banks, in-process materials and final product should be controlled and maintained
- ICH Q7A states that materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination

Holding and Distribution

- Subpart H: Holding and Distribution

  21 CFR 211.142 (b) "Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected."

Holding and Distribution

- Biological Products: General 600's
  - 21 CFR 600.15, "The following products shall be maintained during shipment at the specified temperatures," for example:
    - Cryoprecipitate AHF -18 °C
    - Fresh Frozen Plasma -18 °C or colder
    - Rubella and Mumps Vac. 10 °C or colder

Holding and Distribution

- Advisory Committee on Immunization Practices released recommendations on handling and storage of immunobiologics
- USP<797>Pharmaceutical Compounding – Sterile Preparations
  - Monitoring Controlled Storage Areas
  - Packaging, Handling, and Transportation

Holding and Distribution

- ICH Q7A
  - Storage and Distribution: Warehousing, Facilities should be available for storage of all materials under appropriate conditions
  - Distribution Procedures: Special transport or storage conditions for an API or intermediate should be stated on the label and the manufacturer should ensure that the contract acceptor for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

Holding and Distribution

- Examples of a break in the Chain:
  - Cold room temperature out of range for one week. Intermediate was used and final product did not meet specifications
  - Numerous reports of temperature excursions during shipping of product
    - Delays in Customs Warehouses during international shipments
  - During a –20 °C shipment the vibrations caused a crack in the product container

Cold Storage Equipment Maintenance

- Qualification, maintenance, and control of equipment to ensure cold storage of temperature sensitive products is essential. Examples of critical temperature controlling equipment include the following:
- Cold rooms
- Jacketed manufacturing vessels
- Shipping boxes
- Refrigerated trucks

Cold Storage Equipment Maintenance

- Subpart D Equipment: 21 CFR 211.67(a) "Equipment and utensils shall be cleaned, and maintained..."
- Subpart D Equipment: 21 CFR 211.68(a) "...equipment,...shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance."

Cold Storage Equipment Maintenance

- CGMP of Blood and Blood Components 606's
  - 606.60(b), "Equipment that shall be observed, standardized and calibrated with at least the following frequency, include but are not limited to: Temperature recorder-Daily, Refrigerated centrifuge-observe speed and temperature each day of use"

Cold Storage Equipment Maintenance

- ICH Q7A: For the APIs/final formulated bulk: Records should be maintained, calibration should be performed using standards traceable to certifiable standards, if they exist

Cold Storage Equipment Maintenance

- Examples of a break in the Chain
  - Cold rooms not initially qualified
  - Calibration is missed on temperature probes
  - Chart recorder malfunctions
  - Alarm does not alert operators
  - No documentation for recording, storing and review of temperature monitoring data

Cold Storage and Stability

- The expiration dating of licensed products is based on the stability data collected over time on a product stored within a recommended temperature range
- All of the regulations for equipment used to store stability product samples apply

Cold Storage and Stability

- Subpart I Laboratory Controls/Stability Testing: 21 CFR 211.166(a)(2) “The written program shall be followed and shall include: Storage conditions for samples retained for testing.”

Cold Storage and Stability

- Preamble for Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding
  - all drug products be stored under conditions that are consistent with maintaining stability of the product

Cold Storage and Stability

- ICH Q1a: Stability studies and temperature control
  - Drug Substance/Product (Formal Studies) Primary studies are intended to show that the drug substance/product will remain within specification during the re-test period if stored under recommended storage conditions
  - Storage Conditions: The length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use.

Cold Storage and Stability

- Examples of a break in the Chain
  - Temperature excursions in the cold room used to store stability samples
  - Stability samples stored in QC laboratory refrigerator for one week prior to testing and the refrigerator broke down
  - Contract Manufacturing: Release and stability samples were shipped to the test lab in different shipping containers and transit methods than the final product shipped to the distributor

Evaluation on Inspection

- Temperature specifications for storage of:
  - Critical source materials
  - Product intermediates
  - Bulk/API
  - Product
  - Shipping of intermediates and final product
    - Evaluation of shipping validation
    - Evaluation of routine shipping records and data loggers for shipment of product

Evaluation on Inspection

- Qualification of cold storage equipment based on design specifications
- Daily recording of temperatures
- Procedures for notification of temperature deviations to QA
- Calibration of temperature probes
- Ensure no deviations occurred during storage of product

Conclusion

Bottom line is that every link in the “Cold Chain is critical,” whether it is the storage of a source material, intermediate, bulk/API, final product, or stability sample.

It is critical to maintain safe and effective biopharmaceuticals and it is the law.